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Aortic stenosis and non-cardiac surgery: A systematic review and meta-analysis

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ABSTRACT

Background: Aortic stenosis (AS) poses a perioperative management dilemma to physicians looking after patients who require non-cardiac surgery. The objective of this review is to investigate mortality and adverse cardiovascular events in patients with and without AS who underwent non-cardiac surgery.
Methods: We searched MEDLINE and EMBASE for studies that evaluated mortality and adverse cardiovascular events in patients with and without AS who underwent non-cardiac surgery. Pooled risk ratios for mortality and adverse outcomes (myocardial infarction, stroke, heart failure, death) were calculated using the dichotomous analysis method and subgroup analysis was performed considering the effect of severity of AS and symptoms.
Results: We identified 9 relevant studies with 29,327 participants. Among studies of severe AS, there was no significant difference in mortality (RR: 1.49, 95%CI:0.85–2.61; $P = 0.16$) associated with non-cardiac surgery, but there was a significant increase in the composite adverse outcome (RR: 2.30, 95%CI:1.33–3.97; $P = 0.003$). When the analysis involved any other degree of AS, eight studies were included and the pooled results showed a significant increase in composite adverse outcome (RR: 1.64, 95%CI:1.23–2.19; $P < 0.001$) and myocardial infarction (RR: 1.90, 95%CI:1.54–2.34; $P < 0.001$). When patients with asymptomatic AS were considered, the pooled results of four studies suggested an increased risk of composite adverse outcomes (RR: 1.59, 95%CI:1.19–2.12; $P = 0.002$) but not mortality, myocardial infarction, heart failure or stroke.
Conclusions: Patients with AS undergoing non-cardiac surgery have not been shown to be at increased risk of mortality, but have significantly higher rates of adverse cardiovascular events compared to patients without AS.

1. Introduction

Aortic stenosis (AS) is the most common valve pathology in Europe and North America [1]. It affects 2–4% of the population aged ≥65 years [2] and moderate or severe AS affects 13.3% of adults aged ≥75 years [3]. The annual mortality rate among patients with symptomatic severe AS is 25% with an average survival of 2 to 3 years if not intervened upon [4]. The risk that patients with a history of severe AS presenting for non-cardiac surgery have increased mortality and morbidity rates is still under debate. Hence, the planning and management of surgery may become complicated [5], as severe AS has previously been reported to be a risk factor for poor outcomes in non-cardiac surgery [6,7].

The current American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines on perioperative cardiovascular evaluation and care for non-cardiac surgery [1,8,9] have published recommendations for the management of AS in the context of non-cardiac surgery (based on a level III of evidence, recommendation grade B), but have not considered more recent studies [10–12] that combine advances in anesthetic management for high-risk patients, new anesthetic agents, regional methods, intraoperative monitoring and better perioperative care which limit the relevance of older studies to contemporary practice [13,14].

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Many of the existing studies that form the basis for the recommendations of the current guidelines are limited. For example, despite the severity of AS is recognized as an important contributing factor to outcomes following non-cardiac surgery, several studies did not include it in the analysis [7,12,15,16]. Furthermore, the cardiac risk associated with the surgery itself is often not considered [11,15,17] nor the fitness of a patient for surgery based on American Society of Anesthesiologists (ASA) grade which has been consistently correlated with surgical outcome [18]. There is also considerable variation in the adopted anesthetic technique among the studies, which might affect intra-operative hemodynamics and management. While there are many studies investigating non-cardiac surgery outcomes in patients with a history of AS, these studies are heterogeneous in relation to surgical risk, severity of AS and presence of symptoms, making the results challenging to interpret.

In view of more contemporary work and the importance of systematic revaluation of heterogeneity in individual research, we conducted a systematic review and meta-analysis of studies that evaluated outcomes among patients with and without AS who underwent non-cardiac surgery.

2. Material and methods

We conducted a systematic review and meta-analysis of available evidence comparing patients with different severity of AS undergoing non-cardiac surgery with counterparts free of aortic valve disease for adverse cardiovascular events and mortality.

2.1. Search strategy

We searched MEDLINE and EMBASE from conception (1946 for MEDLINE and 1974 for EMBASE) up to December 2015 (Ovid SP) with no language limitations using the search terms in Supplement 1.

2.2. Study selection and extraction

We only found observational studies, which evaluated mortality and adverse cardiovascular events in patients with AS who underwent non-cardiac surgery. Full inclusion and exclusion methodology are shown in Supplement 1.

Two authors (CSK and MR) independently screened titles and abstracts of studies found on the search for potentially relevant studies. Any uncertainty about inclusion was resolved by a third reviewer (RB or MAM). Potentially relevant studies were downloaded and final inclusion was determined after reviewing the full text of the study. Two authors (CSK and MR) extracted data from full texts onto pre-specified tables that included elements on study design, participants, participant selection criteria and results (including statistical adjustment). The data extracted were then checked (in an unblinded manner) by at least one other reviewer (RB or MAM).

2.3. Quality assessment

The quality of the studies was determined by considering if the sample size was >100 participants in each arm, if the methods used to ascertain and grade the severity of AS was reliable, if the selection of control group was appropriate, if the method of determining outcomes was reliable, if loss to follow up was low and if adjustments were used in the analysis. If there were >10 studies available in the meta-analysis, with no evidence of substantial statistical heterogeneity, we aimed to generate funnel plots to assess the possibility of publication bias [19].

2.4. Data analysis

Data analysis was performed using RevMan 5.3 (Nordic Cochrane Centre). Random effects meta-analysis was performed using the dichotomous analysis method. Statistical heterogeneity was assessed using I^2 statistic [20], with I^2 values of 30–60% representing a moderate level of heterogeneity. The primary analysis included only participants with severe AS and secondary analysis included any degree of AS. Pre-specified subgroup analysis was performed by evaluating studies of asymptomatic and symptomatic AS, clinical status (emergency and elective surgery), severe and non-severe AS and cardiac risk index. We performed additional sensitivity analysis to evaluate the influence of coronary artery disease (CAD) on adverse outcomes in patients with and without AS who undergo non-cardiac surgery. Subgroups studied were those with no difference in the reported prevalence of CAD or myocardial infarction between the AS and control group and based on prevalence of <10% versus >10% and <30% versus >30% in the study cohort. In addition, we explored the differences in age, renal failure and comorbidities on patient with AS and control group and its effect on adverse outcomes.

3. Results

3.1. Study selection

Nine studies met the inclusion criteria [7,10–12,14–17,21]. One study evaluated progression of AS but was not included in the meta-analysis because it did not evaluate cardiovascular outcomes or mortality [12]. The process of study selection is shown in Supplementary Fig. 1.

3.2. Study characteristics

All of the included studies were retrospective in design and 3 were cohort studies while 6 were case-control in design (Table 1). The sample size of included studies ranged from 44 to 15,433 participants and the total number of participants was 29,327 (mean age 74 years, 51% male). Study cohorts were derived from USA, Demark, Netherlands, Ireland, Japan and Canada and were published between 1991 and 2011.

3.3. Study quality assessment

All studies except two had >100 participants in each arm (Table 1). In general, reliable methods for ascertainment of AS were used either through echocardiography or use of International Statistical Classification of Diseases (ICD) codes. Two studies [11,14] used propensity score matching while five studies [7,10,16,17,21] used matching based on study variables and two included unselected participants [12,15]. A variety of methods were used to ascertain outcomes including electronic patient records, national registries, medical charts and telephone contact. One study [17] matched for age and gender and another study [7] matched for year and type of surgery. Only one study [16] adjusted for confounders including age >65 years, presence of CAD, congestive heart failure, diabetes mellitus and hypertension.

3.4. Study results

The definition and severity of AS, anesthetic used, and results are shown in Table 2. A variety of different parameters were used for the grading of AS, which included echocardiography parameters such as valve area, trans-aortic valve flow velocity and mean trans-valvular pressure gradient. Three studies did not report the type of anesthesia used [11,14,16] and two studies included only patients undergoing surgical procedures under general anesthesia [10,12]. The remaining studies comprised a combination of general and regional anesthetic techniques. The outcomes evaluated included mortality, composite adverse cardiovascular events, myocardial infarction, heart failure, stroke, length of stay, receipt of prolonged intubation or re-intubation and intensive care admission. All but one study defined the non-cardiac surgery (Supplementary Table 1) and only one study was exclusive to hip operations [15]. Supplementary Table 2 shows outcome data analysis of those studies linking the presence or not of symptoms of AS with the intrinsic surgical risk of any given non-cardiac surgery.

Selections of studies were pooled together based on specific variables and a sub-group, variable-specific analysis of the outcome was performed. Five case-control studies [7,10,14,15,17] enrolling only patients with severe AS were pooled and included in the meta-analysis (Fig. 1). The analysis suggests that severe AS is associated with a significant increase in composite adverse outcome as reported by each individual study (RR 2.30 95% CI 1.33–3.97, 4 studies, $I^2 = 66\%$) but not specifically for mortality, myocardial infarction, heart failure or stroke.

Eight studies enrolled patients with AS of any degree of severity [7,10,11,14–17,21]. In keeping with the results of each individual study, the pooled analysis of 6 of them illustrated a significant increase in composite adverse outcome (RR 1.64 95% CI 1.23–2.19, $P < 0.001$) as well as a significant increase of myocardial infarction (RR 1.90 95% CI 1.54–2.34, $P < 0.001$) (Fig. 2). There were two pooled studies where appeared to be